REMARKS

Claims 28-32, 38 and 39 are pending. Claims 40-43 have been added. Applicant respectfully requests that the foregoing amendments be made prior to examination of the present application, and respectfully requests reconsideration of the present application in view of the foregoing amendments and the reasons that follow. This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, along with appropriate defined status identifiers. Claims 28-32 and 38-43 are presented for further consideration.

Claims 28-32 and 38-39 are rejected under Section 102(b) based on Leung *et al.* US 5,789,554. This document is not effective as a reference against the present application, as detailed in applicant's previous response. More particularly, the instant application is a continuation of USSN 09/741,843, filed 12/22/00, which was a continuation of USSN 09/127,902, filed 8/3/98 (now U.S. Patent No. 6,187,287), which was a continuation of USSN 08/690,102, filed 7/31/96 (now U.S. Patent No. 5,789,554), which was a continuation of USSN 08/289,576, filed 8/12/94. Support for the instant claimed subject matter may be found going back to the original priority document, USSN 08/280,576, filed 8/12/94, as detailed below in response to the written description rejection.

The examiner indicates that the oath or declaration is defective, based on his belief that the present application is a continuation-in-part application. Based on the following discussion with respect to the rejection under Section 112 for lack of written description, applicant maintains that present application is a continuation which is entitled to the priority date of application serial no. 08/289,576. Therefore, a new oath or declaration is not required.

Claims 28-32 and 38-39 are rejected under Section 112, first paragraph, as failing to comply with the written description requirement. The examiner urges that applicant is claiming a subgenus of humanized antibodies, but disclose only a single monoclonal antibody, LL2. The examiner cites *In re Gosteli* as holding that disclosure of two chemical compounds within a subgenus did not describe that subgenus. *Gosteli* was an attempt to claim the right of foreign priority for a subgenus claim reciting a total of 21 specific compounds. The foreign priority document disclosed only two compounds within the subgenus. The CAFC found that the two compounds were an inadequate written description of the subgenus of 21 compounds.

The examiner also cites *Enzo Biochem* 323 F3d at 966 and 63 USPQ2d at 1615, commonly referred to as "*Enzo II.*". *Enzo* involved a US patent claiming nucleic acid probes that preferentially hybridize to the DNA of *Neisseria gonorrhoeae*, which causes gonorrhea, over the DNA of *N. meningitidis*, which causes meningitis. In *Enzo I*, the CAFC held that an inventor must obtain a new compound and resolve its structure before he or she is entitled to patent it. The Federal Circuit reversed itself on rehearing (*Enzo II*). In the opinion, the Federal Circuit referred back to the *Eli Lilly (119 F.3d 1559 (Fed. Cir. 1997))* case where it had considered claims to genetic material that had only been defined by function, and found that the functional description alone was insufficient to satisfy the written description requirement. However, the Federal Circuit clearly stated that not all functional descriptions of genetic material would fail to meet the written description requirement, particularly not when functional characteristics are coupled with a known or disclosed correlation between function and structure.

The examiner also cites *Noelle v. Lederman*, 69 USPQ 2d. 1508 (Fed. Cir. 2004). Claim 1 of Lederman's patent is directed to "a monoclonal antibody, which specifically binds and forms a complex with the 5c8 antigen located on the surface of activated T cells and thereby inhibits T cell activation of B cells, the 5c8 antigen being an antigen to which monoclonal antibody 5c8 (ATCC Accession No. HB 10916) specifically binds." The court stated that:

> The invention is, for purposes of the "written description" inquiry, *whatever is now claimed. Vas-Cath,* 935 F.2d at 1563-64 (emphasis in original). Thus, the test to determine if an application is to receive the benefit of an earlier filed application is whether a person of ordinary skill in the art would recognize that the applicant possessed what is claimed in the later filed application as of the filing date of the earlier filed application. An earlier application that describes later-claimed genetic material only by a statement of function or result may be insufficient to meet the written description requirement. *See Regents,* 119 F.3d at 1566. This court has held that a description of DNA "'requires a precise definition, such as by structure, formula, chemical name, or physical properties,' not a mere wish or plan for obtaining the claimed chemical invention." *Id.* (quoting *Fiers v. Revel,* 984 F.2d 1164, 1170 (Fed. Cir.1993)). Therefore, this court has held that statements in the specification describing the functional characteristics of a DNA molecule or methods of its isolation do not adequately describe a particular claimed DNA sequence. Instead "an adequate written description of DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." *Id.* at 1566-67 (quoting *Fiers,* 984 F.2d at 1171).

Each of the three cases relate to patents or applications in which the claimed invention was a product. In clear contrast, the present claims are directed to a method. The present method claims are therefore readily distinguishable on the facts from the cited cases. As noted in *Enzo II*, citing *Vas-Cath*, "the invention is, for purposes of the "written description" inquiry, *whatever is now claimed*." Therefore, the proper inquiry is "whether a person of ordinary skill in the art would recognize that the applicant possessed what is claimed in the later filed application as of the filing date of the earlier filed application" (*Enzo II, supra*). The original specification, as filed on August 12, 1994, clearly informs a person of ordinary skill in the art that applicant possessed a method for humanizing antibodies in which each variable (V) region framework (FR) sequence of a non-human antibody is compared to a corresponding variable (V) region framework (FR) sequence of a human antibody to determine the degree of sequence homology between the non-human antibody FRs and the human antibody FRs, and then each FR in the non-human antibody is replaced with a human antibody FR which exhibits sequence homology to the non-human antibody FRs. Thus, the specification discloses:

> By comparing the murine variable (V) region framework (FR) sequences of LL2 to that of human antibodies in the Kabat database (Kabat *et al.*, Sequences of Proteins of Immunological Interest, 5th ed., U.S. Department of Health and Human Services, U.S. Government Printing Office, Washington, D.C.), which is incorporated by reference, the human REI (FIG. 1A, SEQ ID NO. 6) and EU (FIG. 1B, SEQ ID NOS. 9 and 8) sequences were found to exhibit the highest degree of sequence homology to the FRs of VK and VH domains of LL2, respectively. Therefore, the REI and EU FRs were selected as the human frameworks onto which the CDRs for LL2 VK and VH were grafted, respectively. The FR4 sequence of NEWM, however, rather than that of EU, was used to replace the EU FR4 sequence for the humanization of LL2 heavy chain. Based on the results of computer modeling studies (FIGS. 2A and 2B), murine FR residues having potential CDR contacts, which might affect the affinity and specificity of the resultant antibody, were retained in the design of the humanized FR sequences (FIG. 1).

It is clear that each variable region framework sequence was compared to its corresponding framework region in a database of human antibodies, and that replacement of framework regions was based on sequence homology. This is the invention claimed in the present application and the specification shows that applicant possessed this invention as of their earliest filing date.

Applicant is not presently claiming a genus of humanized antibodies, but rather a method for designing humanized antibodies. Thus, quotations in the Action that "a patentee will not be deemed

to have invented species sufficient to constitute a genus by virtue of having disclosed a single species when...the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed" are not on point.

Applicant's invention provides a method of producing humanized antibodies, and applicant has used this invention to produce other humanized antibodies, as summarized in the following table.

Antibody	Variable domain	FR1	FR2	FR3	FR4	Disclosed in
hLL2	VH	EU	EU	EU	NEWM	Present application
	Vk	REI	REI	REI	REI	US 5,789,554
hMN3	VH	EU	EU	EU	KOL	WO04029093A2
	Vk	REI	REI	REI	REI	
hMu9	VH	EU	EU	EU	NEWM	US 20050169926A1
	Vk	WOL	WOL	WOL	WOL	
hL243	VH	RF-TS3	RF-TS3	RF-TS3	NEWM	US 20060210475
	Vk	REI	REI	REI	REI	
hLL1	VH	RF-TS3	RF-TS3	RF-TS3	NEWM	US 20040115193A1
	Vk	HF-21/28	HF-21/28	HF-21/28	HF-21/28	

Applicant also has disclosed other antibodies humanized by the method presently claimed. For example, US 7,109,304 disclosed a humanized anti-CD19 antibody and US 7,151,164 discloses a humanized anti-CD20 antibody (hA20). US 20040191248 discloses humanized anti-CEA antibody (hMN14). US 20040235065A1 discloses humanized anti-AFP (Immu31), which is also described in Qu *et al.*, "Humanization of Immu31, an alpha-fetoprotein-specific antibody," *Clin Cancer Res.* Oct;5(10Suppl):3095s-3100s (1999). WO03074566A2 discloses humanized anti-EGP-1 (RS7). Applications subsequently filed by Leung, US20030040606A1 and US20050033028A1 (Examiner: David Blanchard) also disclose production of humanized antibodies by the presently claimed method, as do articles by Leung *et al.* (Leung *et al.*, *Hybridoma* v13:469-

475 (1994) and Leung *et al.*, *Molecular Immunology*, v32:1413-1427 (1995)). Thus, the method has been a useful tool for producing humanized antibodies generally.

If there are any problems with this response, or if the examiner believes that a telephone interview would advance the prosecution of the present application, Applicant's attorney would appreciate a telephone call. In view of the foregoing, it is believed none of the references, taken singly or in combination, disclose the claimed invention. Accordingly, this application is believed to be in condition for allowance, the notice of which is respectfully requested.

Respectfully submitted,

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